UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,720	12/30/2003	Philip Jordan Thomas	UTSD:703USD1	7522

7590 02/23/2005

Steven L. Highlander, Esq.
FULBRIGHT & JAWORSKI L.L.P.
Suite 2400
600 Congress Avenue
Austin, TX 78701

EXAMINER	
RIGGINS, PATRICK S	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/748,720	THOMAS ET AL.	
	Examiner	Art Unit	
	Patrick S. Riggins	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence(s) of the specification or in an application data sheet by identifying the prior application by application number (37 CFR 1.78(a)(2) and (a)(5)). If the prior application is a non-provisional application, the specific reference must also include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number. There is no reference to provisional application 60182283 in the first sentence of the specification. To gain benefit of this priority claim, there must be reference to this provisional application.

Specification

2. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

3. The disclosure is objected to because of the following informalities: Sequence rules have not been complied with. See 37 C.F.R 1.821-1.825 for sequence rules. Specifically, the legend for Figure 1A on page 7, line 10 lists the sequence of the HA tag. As this is greater than four

amino acids, it must be included in the sequence listing. Additionally, the three sequences on page 65 require SEQ ID NOs.

Appropriate correction is required.

4. Applicants are reminded of the provisions of 37 C.F.R 1.121(c) regarding proper format of an amendment to the claims.

Claim Rejections - 35 USC § 112-2

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 44-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The last line of claim 44 refers to "said protein." This is vague and indefinite because it is unclear to which protein "said protein" is referring. This could pertain to the "fusion protein" of step (a), the "protein of interest" of step (a)(i), or the "marker protein" or step (a)(ii). As such, this claim is vague and indefinite. As claims 45-57 all depend from claim 44 and thus contain all the limitations of claim 44, they too are vague and indefinite.

Claim Rejections - 35 USC § 112-1

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 44-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for assessing "folding and/or solubility" of a protein and for using expression constructs and cells for expressing fusion proteins and complementing marker fragments to assess protein folding and/or solubility, does not reasonably provide enablement for assessing "stability" of a protein or for utilizing purified proteins for this sort of a protein folding/solubility assay. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

9. Claim 44 defines a method whereby a fusion protein is contacted with a portion of a marker protein, such that if the fusion protein has properly folded, structural complementation will occur and a relative increase in the activity of the marker protein can be detected. The claim suggests that this will allow for the assessment of "protein stability, folding and/or solubility." The entire specification is drawn to showing how this type of protocol would be effective in determining folding and/or solubility of a protein of interest using cells that contain the appropriate genes and express the appropriate fusion proteins:

> Thus, there is provided, a method for assessing protein folding and/or solubility comprising (a) pròviding an expression construct comprising (i) a gene encoding fusion protein, said fusion protein comprising a protein of interest fused to a first segment of a marker protein, wherein said first segment does not affect the folding or solubility of the protein of interest, and (ii) a promoter active in said host cell and operably linked to said gene, (b) expressing said fusion protein in a host cell that also expresses a second segment of said marker protein, wherein said second segment is capable of structural complementation with: ' said first segment, and (c) determining structural complementation, wherein a greater degree of structural complementation, as compared to structural complementation observed with appropriate negative controls, indicates proper folding and/or solubility of said protein.
>
> (Summary of Invention, page 4, lines 15-24).

10. The disclosure as filed does not contain sufficient description to enable one of skill in the art to use this method for assessing protein stability or to practice the determination of protein folding and/or solubility *in vitro* using purified proteins without undue experimentation. A number of factors have been considered in making this assertion that undue experimentation is required to practice this invention as delineated by *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

11. Claim 44 is very broadly drawn as the assay can be with any protein of interest and any marker protein that can be complemented through interaction of separate segments of the protein chain. To determine the stability of a protein, one must measure a known amount of protein with regard to its conformation or assembly over a period of time to monitor for any decrease in assembly over that time period. This type of experiment would normally be performed utilizing some sort of pulse-chase experiment such that a particular subset of proteins could be analyzed over time. The nature of this assay is not accounted for in the present invention because the examples given in the specification all measure the structural complementation that occurs at fixed point in time, essentially taking a snapshot of the structural considerations of the protein of interest. There is no teaching in the specification that would allow the skilled artisan to adapt the present invention to a time course-type of experimental protocol. There would be numerous considerations that would have to be accounted for if the skilled artisan were to attempt such an experimental protocol, such as how could the activity of the marker protein that was being

detected to determine the level of structural complementation taking place be adapted to allow for detection over time, or how the levels of the fusion protein and the complementing fragment of the marker protein could be maintained at a level such that any stabilized level of marker protein activity was not simply due to the synthesis of new protein to replace any that was degrading and thus unstable. These types of issues would all need to be answered experimentally.

12. Additionally, there is no description in the specification of any way to overcome the obvious pitfalls of attempting a mixing assay of this nature using purified proteins. The specification does a fine job of exemplifying the use of gene constructs where the protein of interest is molecularly fused to a segment of a marker protein. This fusion protein is then coexpressed in an appropriate cell that also expresses the complementary fragment of the marker protein. There is no description however, of purifying the proteins and mixing them *in vitro*. The problem with this type of approach is that the likelihood of success of this sort of *in vitro* assay is extremely low. The reason for this is that the protein of interest fused to the appropriate segment of the marker protein would be unlikely to be soluble and thus unlikely to be useful in an *in vitro* assay of this nature. Indeed, the proteins listed in claim 56, are often proteins from disease states that would be unlikely to fold properly in solution. As an example of this: "CFTR NBD1 has been shown to be insoluble, forming inclusion bodies when expressed in *E. coli*" (p68, lines 18-19). "Taken together, these results suggest that in these cases, the relatively small .alpha.-fragment, when fused to a target polypeptide, does not have large effects on the target's solubility; neither increasing that of the otherwise insoluble targets (CFTR-NBDs), nor decreasing that of the partially soluble one (MJ1267)" (page 70, lines 6-9)(emphasis added).

13. How then could these proteins be purified and used in an *in vitro* mixing assay? Quite simply, they could not. Additionally, the assay would never be functional in this regard because even if the proteins were somehow purified, their insolubility would lead to precipitation and inability to properly mix to potentially complement with the complementary segment of the marker protein. There are no working examples given except for those mentioned above that address using cell-based, gene expression-type assays.

14. When determining if an enablement rejection is proper, one first looks to the specification for teachings which would enable the skilled artisan to practice the invention. As delineated above, there is no direction given with regard to adapting the methods of the invention to determine what the stability of the protein of interest was and no direction given with regard to utilizing purified proteins in an *in vitro* assay. If one determines that the specification is not enabling, one then looks to the prior art to determine if the knowledge existed in the art at the time of filing that would enable one to practice the invention. There was no such knowledge with regard to adapting this type of an assay to reading activity over time and no art with regards to how to stably purify these proteins, absent some sort of additional fusion. Following this prior art determination, one then considers the level of experimentation that would be required to practice the invention. As described above, an undue level of experimentation would be required to practice determining protein stability or to utilize purified proteins *in vitro*. Thus, the specification is not enabling for assessing protein stability or for performing an *in vitro* mixing assay using purified proteins. As claims 45-57 depend from claim 44, they all contain these limitations. Therefore, the specification is not enabling for any of claims 44-57.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 44-57 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 and 29 of U.S. Patent No. 6,727,070, respectively. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the patent claim(s). Although the conflicting claims are not identical, they are not patentably distinct from each other because in the instant case claims 44-57 are generic to all that is recited in the respective claims of the patent, i.e. the patented claims fall entirely within the scope of each of instant claims 44-57.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick S. Riggins whose telephone number is (571) 272-6102. The examiner can normally be reached on M-F 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patrick Riggins, Ph.D.
Examiner
Art Unit 1636

JAMES KETTER
PRIMARY EXAMINER